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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,983	11/07/2001	Keith D. Allen	R-517	9383

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	10

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No. 10/005,983	Applicant(s) ALLEN ET AL.	
	Examiner Celine X Qian	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *11,13,23 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12 and 14-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-24 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the inventions of Groups I-IV are closely related; hence a search of all the groups would not be a serious burden. This is not found persuasive because the inventions of Groups I-IV are patentably distinct for reasons set forth of the record mailed on 2/11/03. A search of one group would not be co-extensive with a search of another group, and a search of all the groups in a single application would have been burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 11, 13, 23 and 24 are withdrawn from consideration for being directed non-elected subject matter. Claims 1-10, 12 and 14-22 are currently under examination.

Claim Objections

Claim 12 is objected to as being dependent upon a non-elected base claim (11). But for the purpose of examination, the limitations of claim 11 will be read into claim 12. Applicant is advised to rewrite the claim in independent form including all of the limitations of (non-elected) base claim (11).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-10, 12 and 14-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a heterozygous knockout mouse comprising a disruption in one copy of PERK gene which result in non expression of the gene, wherein there is one functional PERK allele that produces functional PERK protein, and exhibiting phenotypic features including increased susceptibility to seizure as compared to wild type mice, a method of producing such a transgenic mouse by homologous recombination in mouse ES cell, and a cell isolated from the knockout mouse, and method of using said mouse to screen an agent that ameliorates a phenotype of said mouse, does not reasonably provide enablement for other transgenic and/or knockout animal comprising any disruption in the PERK gene. Further, the specification is not enabling for a knockout mouse comprising any disruption in the PERK gene and for any cell comprising any type of disruption in a PERK gene and methods of using said mouse or cells. Moreover, the specification is not enabling for a transgenic mouse having homozygous disruption in the PERK gene wherein said mouse dies within 1-2 days. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to

make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 3-10, 12 and 14-22 are drawn to a cell comprising a disruption in a PERK gene, a non-human transgenic animal comprising a disruption in a PERK gene, a cell from that transgenic animal, a method of producing a transgenic mouse with any disruption in the said gene. The claims are further drawn to methods of using said transgenic animal to screen for agents that modulate the function/expression of the PERK or ameliorate a phenotype of the PERK knockout mouse. Thus, the nature of the invention is directed to transgenic animals and methods of producing and using said transgenic animals.

Breadth of Claims:

In the instant case, the claims 3-10, 12 and 14-22 encompass any transgenic animal containing any disrupted allele for the gene that encodes the PERK. Further, the claims encompass both heterozygous and homozygous knockout mouse comprising any disruption in the PERK gene and exhibiting the phenotypes of perinatal lethality, congenital abnormality and increased susceptibility to seizure as compared to wild type mice. Further, the claims encompass any cell comprising any disruption in the PERK gene and method of producing PERK knockout mouse by using any type of cell comprising a disruption of the PERK gene. The disruption, as disclosed in the specification (page 7, lines 19-28) includes any insertion, deletion or substitution in any portion of the gene (introns, exons, regulatory regions). The claims, therefore, encompass all such disruptions and also cover all animals that contain the PERK gene disruption (page 7, lines 18-28, and page 8, lines 1-5).

The specification does not provide an enabling disclosure for the full scope of transgenic animals of the type claimed. The only embodiment enabled by the specification within the scope of claims 3-10, 12 and 14-22 is for a heterozygous knockout mouse comprising a disruption in one copy of PERK gene which result in non expression of the gene, wherein there is one functional PERK allele that produces functional PERK protein, and exhibiting phenotypic features including increased susceptibility to seizure as compared to wild type mice, a method of producing such a transgenic mouse, and a cell isolated from the knockout mouse, and method of using said mouse to screen an agent that modulates the expression/function or ameliorate a phenotype of said mouse. Thus the breadth of the claims is very broad and encompasses any transgenic animal and a knockout mouse with any disruption in the PERK gene and includes any and all mutant forms, substitutions, deletions, or insertions in the PERK gene, and method of using said animal for screening agents modulate expression/function of the PERK gene.

Amount of guidance in the specification and Working Examples:

The specification discloses a PERK transgenic knockout mouse, wherein the homozygous knockout mouse exhibits phenotype that include congenital abnormality of hydrocephaly which leads to perinatal lethality, whereas the heterozygous knockout mouse exhibits increased susceptibility to seizure compared to wild type mice.

The specification and the working examples provide sufficient guidance to use the invention of a heterozygous knockout mouse comprising a disruption in one copy of PERK gene which result in non expression of the gene, wherein there is one functional PERK allele that produces functional PERK protein, and exhibiting phenotypic features including increased susceptibility to seizure as compared to wild type mice. The specification does not teach how to

make and use the invention with other species of transgenic or knockout animals and with any knockout mouse with any form of disruption in the gene encoding PERK protein, as claimed in the claims 3-10, 12 and 14-22. Further, the specification does not teach how to make and use any cell comprising any type of disruption in the PERK gene as claimed. The specification also fails to teach how to use the homozygous knockout mouse to screen for agents that modulate the expression or function of the PERK. It is unclear how such agents can be screened by using the homozygous knockout mouse since the homozygous mouse does not produce functional PERK gene or protein. The specification further fails to teach how to screen for agents that ameliorate a phenotype of the homozygous mouse. The specification discloses that the homozygous mouse dies within 1 to 2 days. Thus whether the homozygous mouse can be used to for screening test is unpredictable. The scope of claims 3-10, 12 and 14-22 thus surpasses that enabled by the specification.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention with any and all transgenic animals as claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a heterozygous knockout mouse comprising a disruption in one copy of PERK gene which result in non expression of the gene, wherein there is one functional PERK allele that produces functional PERK protein, and exhibiting phenotypic features including increased susceptibility to seizure as compared to wild type mice. However, neither the specification nor the working examples

provide enough guidance on how to practice the invention with any and all transgenic animals and/or transgenic mice carrying any and all transgene(s) of the types recited in the claims.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification only discloses the phenotype of the PERK gene knockout mouse but fails to disclose the phenotypes of any and all knockout animals with a disruption in the PERK gene. Given the state of the art, the phenotype of any transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals, including mice, that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification.

Further, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). Thus, the disclosure, while being enabling for a heterozygous knockout mouse containing one disrupted alleles for the gene encoding the PERK, does not provide sufficient support to predict the same phenotype in other animal systems.

The particular genetic elements required for expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, the phenotype of knockout animals is not predictable. For example, Jacks et al. (1992) describe Rb knockout mice that do

not display retinoblastoma; rather they exhibit the unexpected phenotype of pituitary tumors. The pituitary tumors arise from cells lacking a wild-type Rb allele. Thus, tumors were found to arise not in retinas, as in humans, but in the pituitary gland (page 299, Discussion, paragraphs 1 and 3). Therefore, in the absence of specific guidance and working examples, the phenotype of transgenic animals with the scope as claimed is unpredictable. In such a situation, one skilled in the art would not know how to make and use the invention as claimed, without undue experimentation.

The specification fails to provide an enabling disclosure for the preparation of other species of knockout animals besides mice having a disruption in the PERK gene because the guidance offered in the specification is limited to the preparation of mice harboring such mutations and no teachings or guidance are offered in regard to how one would have prepared any other type of animal having the recited gene disruption. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out the method. The prior art does not teach the generation of a transgenic mouse from any other types of cells. The only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully

demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. S38, column 1, paragraph 1). Thus, knockout animals cannot be prepared for any species other than the mouse. Since ES cell technology was required to produce the claimed animals and practice the claimed methods of using such animals, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals and to practice the claimed methods in species other than mice.

In view of the limited guidance in the specification, and limited working examples directed to transgenic, knockout mice with a specific knockout gene and exhibiting a specific phenotype, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to make and use the invention in its full scope as claimed. Thus, the enabled scope of the claims is limited to a heterozygous knockout mouse comprising a disruption in one copy of PERK gene which result in non expression of the gene, wherein there is one functional PERK allele that produces functional PERK protein, and exhibiting phenotypic features including increased susceptibility to seizure as compared to wild type mice.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 8, 12, 14 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1 and 2, the term "selectable marker," renders the claims indefinite because it is unclear how a marker protein can be part of a vector construct. It is recommended to use terms such as "selectable marker gene."

Regarding claims 1 and 2, it is unclear how the target construct is arranged. In other words, is the first polynucleotide adjacent to the second polynucleotide or there is a selectable marker in between? In addition, it is also unclear whether the first and second polynucleotide is a contiguous sequence of the target gene or just portions of the target gene. The arrangement of the elements is essential to the operability of the invention.

Regarding claims 8, 12 and 21, the word "derived" renders the claim indefinite because the nature and number of derivative processes is unknown. Use of the term "isolated" is suggested.

Regarding claim 14, the term "significant expression" renders the claim indefinite because it is unclear what level of expression is considered to be significant. As such, the metes and bounds of the claim cannot be established.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5 rejected under 35 U.S.C. 102(a) as being anticipated by Harding et al.(2000, Molecular Cell, Vol. 5, pages 897-904).

Harding et al. disclose a PERK targeting construct comprising a first polynucloetide homologous to a first portion of the PERK gene, a second polynucleotide to a second portion of the PERK gene and a selectable marker gene, and method of producing said target construct obtaining said polynucleotides and inserting the polynucleotides into a vector (see page 898, Figure 1 and page 902, 2nd col., last paragraph). Harding et al also disclose murine embryonic stem cell comprising said construct (see page 897, 2nd col., 1st paragraph of Results section). Therefore, Harding et al. disclose the instantly claimed inventions.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
April 18, 2003

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER